Trans-NIDDK

September 2002 Council

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GENETIC MODIFIERS OF MENDELIAN DISEASES

FY 2003 Action

The objectives of this RFA are to stimulate research to identify and characterize the modifier genes responsible for variation in clinical phenotype and progression of Mendelian diseases within the mission of NIDDK. Identification of the genes responsible for these differences would lead to better understanding of disease pathogenesis, early diagnosis, and improved treatment.

Background

All diseases are variable in their presentation due to differences in the genetic makeup and the environmental exposure of the affected individual. For disorders inherited in a Mendelian fashion, a single gene plays the predominant role in the development of a disease phenotype. However, phenotype variation occurs even among those who have identical genotypes at a disease locus. To further our understanding of the molecular basis of monogenic disorders, it will be necessary to find other genes that contribute to phenotype variability.

In FY 2001, the NIDDK cosponsored an RFA, "Genetic Modifiers of Single Gene Defect Diseases," sponsored by NHLBI for heart, lung and blood diseases. NIDDK was able to fund two grants from this initiative that were of interest to this Institute. However, diseases affecting the liver and kidney as well as metabolic diseases were not included in the scope of the RFA. For FY 2002, NIDDK has organized a meeting on this topic highlighting diseases of interest to NIDDK including cystic fibrosis, Gaucher's Disease, hemochromatosis, Beta-thalassemia, Hirschsprung disease and polycystic kidney disease that will be held September 9 and 10, 2002. In FY 2003, NIDDK proposes to issue an RFA to identify genetic modifiers in all of the conditions relevant to our mission. The identification and characterization of modifier genes will clarify the process of pathophysiology, enable more accurate prognosis, early diagnosis, and may provide novel, and possibly, more accessible therapeutic targets, that are more useful than the gene primarily involved in causing the disease.

Research Goals and Scope

This initiative is intended to solicit research grant applications to identify the modifier gene or genes responsible for variation in the clinical progression and outcome of genetic Mendelian diseases of interest to NIDDK. The approaches to identify these genes can include genetic mapping, positional candidate cloning, and positional cloning to identify the gene, characterize the allelic variants of the gene(s) identified, and to demonstrate that the variation in the gene(s) is responsible for phenotype variation.

One powerful method to demonstrate the effect of modifier genes has been using mouse models of genetic diseases. By breeding the genetic defect on different background strains of mice, the severity of the phenotype of the genetic disease can be altered. This approach has been used to identify regions that may contain genetic modifiers. This approach will become more powerful as the sequence of different mouse backgrounds becomes available to analyze.

Careful phenotyping of patient populations has also lead to the identification of genetic modifiers. For these studies, the applicants must be able to demonstrate the availability of well-

characterized patient population in which the variation can be demonstrated.
Genotype/phenotype studies may be performed to reveal the degree to which disease severity can be attributed to allelic differences or gene environment interactions.

THE NIDDK CENTRAL REPOSITORIES

FY 2003 Action

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) is developing contracts to establish central NIDDK facilities for archival storage of biosamples and data collected in large, multi-site studies and for processing of genetic samples collected in these studies.

Background

The NIDDK funds and oversees a large number of multi-site studies and clinical trials. In response to a determined need, the NIDDK decided to set up central NIDDK facilities for archival storage of biosamples and data collected in large multi-site studies. In addition the repository function will include a central genetic sample facility to serve the needs of new studies by providing uniform high quality laboratory and archiving services. Central archival repositories will enhance the value of large studies by increasing access to the biosamples and data that have been collected. Investigators seeking to reanalyze biosamples or data from large NIDDK-funded studies will be able to direct their inquiries to a single central entity, rather than to numerous laboratories with individual storage and access policies. Thus when appropriate, researchers will be able to obtain samples expeditiously and more efficiently. The sample, genetics, and data repositories will allow resources to be shared by the research community, while protecting the rights of subjects. This will expedite discoveries into the causes and treatments of the diseases that are the focus of NIDDK-funded research. The availability of shared resources from repositories encourages work by junior investigators, investigators with novel approaches, and others not included in current collaborations, without excluding those who are established in their fields. As a result, repositories ensure that research participants make a maximal contribution, and decrease duplicative sampling efforts. The NIDDK Central Repositories will also serve as a standard of quality and bioethics as this field evolves.

Research Goals and Scope

The repositories will serve thee separate functions:
1) Biosample repository – gathering, storing and distributing samples from studies. The repository will work with investigators in new and ongoing studies to implement an appropriate labeling, aliquoting and storage system that will facilitate the transfer of the biosamples. In some instances, the repository may be directed to acquire samples from studies already completed.
2) Data repository – consulting with new and ongoing studies to prepare research data for eventual use by others. Gathering, storing and distributing the completed finished datasets associated with archived biosamples from completed studies and helping researchers carry out searches of stored datasets.
3) Genetics repository – providing support services for genetics studies including cell line immortalization, DNA extraction and storage.

ANCILLARY STUDIES TO RENAL CLINICAL TRIALS

FY 2003 Action

It is planned to facilitate the more complete utilization of the existing renal clinical trial infrastructure by encouraging proposals for ancillary studies.

Background

The Division of Kidney, Urologic and Hematologic Diseases, through our clinical trials programs, supports the creation of a number of well-characterized patient cohorts. In a number of cases, these cohorts of patients could be used for additional research beyond the primary study. In some cases additional studies could be performed utilizing primarily the data and specimens collected in the course of the primary study, but in other cases additional patient information could be effectively acquired. In many cases, it is anticipated that such projects would originate from within the steering committee of the primary study, but in some cases an outside investigator could initiate such a project, generally in collaboration with a primary grantee. We currently fund a small number of ancillary studies to existing trials, but in general believe that the resources represented by these patient cohorts are incompletely utilized. The intent of this initiative is to encourage the identification and critical review of ancillary studies to existing and recently completed trials.

We have identified the following barriers to R01 grants utilizing clinical trial cohorts: (1) lack of widespread awareness of existing resources; (2) standing study sections provide an inhospitable review climate for this kind of work because of the small number of clinical investigators and lack of detailed knowledge of primary projects; and (3) need for grantees to develop appropriate partnerships with primary grantees.

Research Goals and Scope

It is proposed to develop an inventory of existing resources; new trials in the future will in general utilize the NIDDK repository, facilitating sharing of data and specimens. A meeting of clinical trials investigators will be held to review the existing resources. Following that meeting, it is planned to publish a program announcement encouraging applications. Administrative review would be required prior to submission, to insure adequate cooperation with primary grantees and compatibility with patient protection and original consent. We propose the grants should be reviewed within the Institute, since the trial data is multi-site, and to insure expertise about the relevant trials. A single yearly receipt date will probably be used.

PIMA HEALTH EDUCATION PROJECTS

FY 2003 Action

A video on recommendations from the DPP and culturally-sensitive publications for use in the NIH Clinic and in the community are proposed for FY 2003. These products will raise awareness among the tribe about intervention and prevention of disease, and have the potential to benefit a wider audience among other Native American tribes who also have high rates of diabetes and kidney disease. In FY 2003, we will collaborate with the Native American Working Group of the National Diabetes Education Program in producing materials appropriate for Indian elders and Indian children.

Background

The Pima Indians of Sacaton, Arizona, have the highest rate of diabetes in the world. They have volunteered in NIDDK-conducted epidemiological and genetic studies in diabetes and obesity for over 35 years. Advances from these studies have added significantly to worldwide understanding of the natural history and progress of the disease. In addition, The Gila River Indian Community was a primary site for the Diabetes Prevention Program (DPP) and is also participating in the Look AHEAD trial. Nevertheless, the rate of diabetes and the kidney disease that can follow from it remain high in the community.

Following the successful production of a culturally-sensitive video on organ transplantation in FY 2001, NIDDK has continued to promote understanding of ongoing clinical studies and to empower the Pimas to make healthy lifestyle changes to prevent obesity and the onset of diabetes and its complications through a variety of health education projects. A second successful video on breast feeding, accompanied by a brochure and a calendar were produced in FY 2002 in conjunction with IHS staff.

TRANS-NIDDK
Conferences and Workshops

Ubiquitin and Ubiquitin-like Modifications in Health and Disease
Date: March 24-25, 2003
The meeting will highlight recent advances in the understanding of how ubiquitin and ubiquitin-like modifications affect cell metabolism and gene transcription, protein sorting and signal transduction, and how they mediate protein turnover via the proteasome. The meeting will also examine the role of these modification pathways in normal human physiology and in a number of diseases.